Predictors of Treatment Failure with Sofosbuvir/Daclatasvir Regimen for 12 Weeks in Chronic HCV Egyptian Patients

Thesis

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List of Abbreviations

Abb.	Full term
AFP	*Alpha-fetoprotein*
ALT	*Alanine transaminase*
ARF	*Alternate reading frame*
ART	*Abbott Real Time HCV RNA assay*
AST	*Aspartate aminotransferase*
AUC	*Area under curve*
BMI	*Body Mass Index*
BOC	*Boceprevir*
BT	*Before treatment*
CAP/CTM	*Cobas AmpliPrep /Cobas TaqMan analyzer*
CBC	*Complete blood picture*
CD4	*Cluster of differentiation 4*
CGs	*Cryoglobulins*
DAA	*Direct-acting antivirals*
DAC	*Daclatasvir*
DHS	*Demographic health survey*
DM	*Diabetes mellitus*
E1, E2	*Envelope*
EBR	*Elbasvir*
EC	*Effective concentrations*
EIAs	*Enzyme-linked immuno-assays*
ELISA	*Enzyme-linked immunosorbent assay*
EMA	*European Medicines Agency*
GN	*Glomerulonephritis*
GT	*Genotype*
GZR	*Grazoprevir*
Hb	*Hemoglobin*
HBV	*Hepatitis B Virus*
HCC	*Hepatocellular carcinoma*
HCV	*Hepatitis C virus*
HIV	*Human immunodeficiency virus*

List of Abbreviations Cont...

Abb.	Full term
HLA	*Human Leukocyte Antigen*
HPS/CTM	*High-Pure System/ COBAS TaqMan*
HVRI	*Hypervariable region 1*
IgG	*Immunoglobulin G*
IgM	*Immunoglobulin M*
IL28B	*Interleukin 28B*
INR	*International normalized ratio*
ITP	*Immune thrombocytopenic purpura*
IU/L	*International units per litre*
IV	*Intravenous*
KFT	*Kidney Function Tests*
LDV	*Ledipasvir*
LFT	*Liver Function Tests*
MC	*Mixed cryoglobulinaemia*
MELD	*Model for end-stage liver disease*
MPGN	*Membranoproliferative glomerulonephritis*
mRNA	*Messenger RNA*
NCCVH	*National Committee for Control of Viral Hepatitis*
NCR	*Noncoding region*
NK	*Natural killer*
NS	*Nonstructural protein*
NS5A	*Nonstructural protein 5A*
NS5B	*Nonstructural protein 5B*
NTR	*Nontranslated region*
NULR	*Null response to PEGIFN*
OBV	*Ombitasvir*
ORF	*Open-reading frame*
PAD	*Peripheral arterial disease*
PCR	*Polymerase chain reaction*
PCT	*Porphyria cutanea tarda*

List of Abbreviations Cont...

Abb.	Full term

PEG-IFN..... Pegylated interferon alfa-2a
PI..... Protease inhibitors
PR ..... Partial response
PTV/r ..... Paritaprevir/r
RBV..... Ribavirin
REL..... Relapse
RF ..... Rheumatoid fact0r
RIBA ..... Recombinant immunoblot assay
RNA ..... Ribonucleic acid
ROC ..... Receiver operating characteristic curve
SMV..... Simeprevir
SOF..... Sofosbuvir
SOF/DAC..... Sofosbuvir/Daclatasvir
SVR..... Sustained Virological Response
TLC..... Total leucocytic count
TLV..... Telaprevir
U/S..... Ultrasonography
UNOS ..... United Network for Organ Sharing
UTR ..... Untranslated regions
VEL..... Velpatasvir
WBC..... White blood cells
WHO ..... World Health Organization

INTRODUCTION

HCV infection is one of the main causes of chronic liver disease worldwide ***(Lavanchy et al., 2011).***

The long-term impact of HCV infection, ranging from minimal histological changes to cirrhosis with or without hepatocellular carcinoma (HCC). The estimated number of chronically infected HCV patients worldwide is about 180 million ***(Messina et al., 2015).***

Egypt has the highest national-level HCV prevalence in the world, the percentage of adults aging from 15-59 testing positive on the HCV RNA test is 7% of the Egyptian population ***(Kandeel et al., 2017).***

HCV genotype (GT) 4, is the most common variant in the HCV epidemic in Egypt with more than 90% of infections due to genotype 4 ***(Messina et al., 2015).***

The morbidity of HCV in untreated patients as regard liver cirrhosis, liver cell failure and hepatocellular carcinoma represent a major health problem and economic burden ***(Bruno et al., 2007).***

In 2006, in recognition of the enormity of the HCV problem and burden of disease in Egypt, the Minister of Health established the National Committee for Control of Viral Hepatitis (NCCVH), the available regimen was Peginterferon

alfa (PEG-a), 350000 patients had received therapy with SVR rates for patients treated with the PEG-IFN-α2a and alfa-2b were 54%-59% respectively ***(El-Akel et al., 2017).***

The predictive factors of therapy response are also related to the virus and hosts, and they can be classified as clinical, biochemical, immunologic and genetic factors.

Male gender, advanced liver fibrosis, human immunodeficiency virus (HIV) and HBV coinfection, insulin resistance, poor treatment adherence, high viral load (≥ 600.000 UI/mL) and African ancestry have been related with the failure of interferon (IFN) based therapies, particularly with dual therapy (pegylated interferon and ribavirin) ***(Cavalcante and Lyra, 2015).***

In early clinical trials of interferon and ribavirin, a baseline HCV RNA level over 800,000 IU/ml was found to be associated with a 9% lower chance of cure. Subsequent studies found that patients with high viral load had a 15 to 39% lower chance of achieving an SVR.

Recent advances in drug development have led to a number of direct anti-viral agents (DAAs) which deliver high rates of SVR with substantial improvements in the side effect profiles.

One of these drugs, sofosbuvir (SOF), a potent inhibitor of the HCV NS5B polymerase, has been approved for the treatment of HCV in Egypt since 2014 **(Youssef et.al. 2017).**

These regimens include either single DAA therapy SOF with RBV for 24 wks, or dual DAA combination therapy in the form of simeprevir plus Sofosbuvir, Sofosbuvir/Daclatasvir, Sofosbuvir plus ledipasvir, Grazoprevir/elbasvir and Paritaprevir/ ombitasvir/ ritonavir plus ribavirin for 12 wks ***(EASL, 2016).***

Daclatasvir, another DAA which is one of the NS5A inhibitors which is associated with great results in HCV clearance, also it is pan-genotypic ***(Asselah et al., 2014).***

Patients infected with HCV genotype 4 can be treated with daily dose of Sofosbuvir and Daclatasvir for 12 weeks. Also Sofosbuvir/ Daclatasvir and Ribavirin for 24 weeks can be used for treatment of non-responders to Sofosbuvir based therapy according to ***EASL (2016).***

In November 2015 the NCCVH issued a new protocol in which the Sofosbuvir/Daclatasvir for 12 weeks has been included to treat the Easy to treat Egyptian HCV patients according to the following criteria:

- INR<1.2.
- Serum Albumin > 3.5 gm/dl.
- Platelets Count > 150,000.
- Total bilirubin < 1.2 mg/dl.